the status of the related applications on page 1, paragraph 1 of the specification. Applicants have amended that paragraph to recite the current status of the applications.

The Examiner also rejected the drawings as informal and requested that we file formal drawings. Applicants have included copies of the formal drawings for this application with this response.

Enablement Rejection

The Examiner has rejected claims 16-20 under 35 U.S.C. § 112, first paragraph, as allegedly not enabled. The Examiner states that the claims are directed to a method for treating rheumatoid arthritis in a human subject comprising administering to the subject an IL-12 antagonist (antibody or antibody fragment immunoreactive with IL-12). The specification, she alleges, teaches that IFN-γ is implicated in the development, exacerbation, and/or recurrence of autoimmune conditions and that IFN-γ is associated with multiple sclerosis, IDDM, and rheumatoid arthritis. The Examiner argues that while Examples on IDDM and multiple sclerosis are set forth in the specification, it does not contain sufficient guidance for the treatment of rheumatoid arthritis.

Additionally, the Examiner cites to a references that allegedly shows that antibodies against IL-12 do not have a statistically significant effect on the outcome of arthritis. *Butler, Anti-IL-12 and the anti-TNF antibodies synergistically suppress the progression of murine collagen-induced arthritis, Eur. J. Immunol. 29:2205-2212 (1999).* The Examiner, then, concluded that the claimed invention is not enabled.

Applicants have reviewed the specification and the *Butler* reference. The specification provides teachings on how to use antagonists against IL-12 in the

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treatment of autoimmune diseases, such as rheumatoid arthritis, and why they would work. It states that appropriate dosing regimens include about 0.05 to about 25 mg/kg, preferably about 0.2 to about 2 mg/kg. (Specification, page 4, lines 4-8). It also states that rheumatoid arthritis is an autoimmune condition promoted by an increase in levels of IFN-γ and/or TNF-α. (Specification, page 6, lines 17-19). It further provides that IL-12 is known to induce TNF-α and IFN-γ. (Specification, page 2, lines 10-11 and 22). Thus, reading the specification, the skilled artisan would have no reason to doubt that the treatment protocols in the specification would be useful in the treatment of rheumatoid arthritis.

Additionally, *Butler* cannot establish that the claimed method would not work in the treatment of human patients. In the clinical evaluations of the mouse model (clinical score, paw thickness, and joint damage and hyperplasia) the anti-IL-12 treatment group showed improvement over control animals, even though that difference was not reported as significant. The sample sizes in the *Butler* experiments were so small (9 mice in each group) that only very large treatment differences could have been detected in this study. If *Butler* had conducted the study with a much larger number of mice, Applicants believe that the improvement with anti-IL-12 may have been significant.

Butler used the Mann-Whitney test to evaluate the clinical parameters. The Mann-Whitney test differs from the standard student's t test in that it is distribution free, and does not use the actual values of the variables, but only their relative positions in the rank ordering. The Mann-Whitney test, therefore, is inefficient and lacks power because it does not use all of the information in the data. This inefficiency is especially

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problematic for small sample sizes. *Samuels, Statistics for the Life Sciences, at 256 (1989).* Thus, Applicants believe that the evaluations with only 9 mice in each group are not predictive of clinical benefits of IL-12 in the treatment of rheumatoid arthritis.

Furthermore, there is no requirement in the law of enablement that a patented method produce statistically significant results. Applicants believe that contrary to the Examiner's conclusion, all of the clinical data in the *Butler* reference shows that there was an improvement in the anti-IL-12 treatment group compared to the control group, even if that data was not significant. Thus, *Butler* does not provide credible evidence to rebut the teaching in the specification that antagonists to IL-12 are useful in the treatment of rheumatoid arthritis.

Lastly, Butler is only one of many studies on the role of IL-12 in rheumatoid arthritis. Applicants have enclosed a copy of two articles showing the effect of anti-IL-2 antibodies in well-recognized animal models. Each of these references, contrary to *Butler*, report that antagonism of IL-12 positively impacts the outcome of the arthritis using well-known murine models of the disease. For example, *Joosten, et al.* (*Ann. Rheum. Dis.*, 59(3):196-205, 2000) reports, "IL12 is a pro-inflammatory cytokine during onset of acute SCW arthritis. Balances of proimflammatory and anti-inflammatory cytokines were strongly improved by anti-IL12 treatment." *Joosten* at page 196. In addition, *Malfait, et al.,* (*Clin. Exp. Immunol.*, 111:377-383, 1998) found that "administration anti-IL12 [antibodies] . . . dramatically attenuated the severity of the disease, both clinically and histopathologically." *Malfait* at page 377. Thus, contrary to the Examiner's suggestion, the art does not teach "that anti IL-12 has no statistically

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significant effect on the clinical outcome of disease." Clearly, these teachings in the art, when taken together with the guidance in the specification, enable one of ordinary skill in the art to make and use the present invention.

Conclusion

In view of the these amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims. Should the Examiner not believe that the claims are in condition for allowance, Applicants request that she please contact their undersigned representative at (202) 408-4086 for an interview to discuss the application.

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Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: June 15, 2001

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APPENDIX TO AMENDMENT OF JUNE 15, 2001

AMENDMENT TO THE SPECIFICATION

Page 1, paragraph beginning on line 5:

This application is a divisional of application Ser. No. 08/560,943, filed November 20, 1995, now abandoned; which is a file-wrapper-continuation of application Ser. No. 08/212,629, filed March 14, 1994, now abandoned; all of which are incorporated by reference herein.

AMENDMENTS TO THE CLAIMS

17. (Amended) The method of claim 16, wherein said antagonist is administered in a dose of about 0.05 to about 25 mg/kg.

18. (Amended) The method of claim 16, wherein said antagonist is administered in combination with a pharmaceutically acceptable carrier.

19. (Amended) The method of claim 16, wherein said antagonist is an antibody immunoreactive with IL-12.

20. (Amended) The method of claim 16, wherein said antagonist is an antibody fragment [reactive] immunoreactive with IL-12.

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